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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/757,673	01/10/2001	James M. Wilson	GNVPN.019B1USA	8771

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HOWSON AND HOWSON
ONE SPRING HOUSE CORPORATION CENTER
BOX 457
321 NORRISTOWN ROAD
SPRING HOUSE, PA 19477

EXAMINER	
SHUKLA, RAM R	
ART UNIT	PAPER NUMBER
1632	7

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/757,673	WILSON ET AL.	
	Examiner	Art Unit	
	Ram Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 7-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 7-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 10 January 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 7-17 are pending in the instant application.

2. Regarding preliminary amendment filed 1-10-01, it is noted that the abstract was not present with the amendment and therefore, it could not be entered in the application.

Priority

3. It is noted that newly presented claims 12-17 entered by preliminary amendment recite the phrase/embodiment "wherein the level of contaminating adenoviral helper virus is no greater than that obtained by subjecting said recombinant AAV to four rounds of cesium chloride gradient centrifugation" which would encompass "equal to" or "less than" levels of contaminating adenoviral helper virus in claimed composition compared to the level of adenoviral helper virus contamination obtained after four rounds of cesium chloride centrifugation. However, the specification does not provide written support for this phrase or for "less than levels of contaminating adenoviral helper virus". It is noted that the specification only discloses a composition after purification by four rounds of cesium chloride gradient centrifugation. Accordingly, the phrase/embodiment "wherein the level of contaminating adenoviral helper virus is no greater than that obtained by subjecting said recombinant AAV to four rounds of cesium chloride gradient centrifugation" is assigned 11-2-01 as the priority date.

Claim Objections

4. Claims 7 and 11- 13 are objected because they do not consistently use one abbreviation for one term, a recombinant adeno-associated virus. Claims 7 and 11 use the abbreviation rAAV, whereas claims 12 and 13 use the abbreviation recombinant AAV. Consistent use of one term is suggested for clarity.

5. Claim 11 is objected because it has the abbreviation rAAV typed after the term "transgene" in place of being after the term "recombinant adeno-associated virus" as used in claim 7.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 8, 9, and 12-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is indefinite because it recites the phrase "wherein the transgene is a secretable protein". It is noted that a transgene is a nucleic acid which encodes a protein therefore it can not be a protein.

Claims 12 and 13 are vague and indefinite because it recites the phrase "wherein the level of contaminating adenoviral helper virus is not greater than that obtained by subjecting said recombinant AAV to four rounds of cesium chloride gradient centrifugation." It is noted that the specification does not disclose what would considered the contaminating levels of adenoviral helper virus in the recited recombinant AAV composition of claims 12 and 13 and therefore, the metes and bounds of the claimed invention are not clear.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 7-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,866,552 (Wilson JM et al., 2-2-1999). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims 1-4 of the cited patent are drawn to a method of transducing a skeletal muscle cell (which can be interpreted as an isolated cell in vitro or inside an animal), wherein the protein is a secreted protein and the protein is selected from a list of proteins and the virus comprises 5' and 3' ITRs and a transgene operably linked to sequences controlling expression of the transgene in the cell. Claims 7-11 of the instant are also drawn to the similar invention except that claim 7 recites a method of expressing a transgene in a skeletal muscle cell and where as claim 11 recites a method of delivering a transgene to an animal by administering the virus intramuscularly. Regarding the claims 12-17 it is noted that the cited patent teaches recombinant AAV purified by four rounds of cesium chloride density gradient centrifugation (see colum 8, example 1, lines 44-61), therefore, the AAV recited in claims of the cited patent would encompass the AAV of claims 12-17 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 7-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9, 20, 21, 23, 25, 26, and 27 of co-pending Application No. 09/237,064. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method for expressing a transgene in an an animal/patient/cell by administering a composition comprising an adeno-associated viral vector comprising a transgene that encode ApoE, factor IX, erythropoietin etc. to the cell or to the animal intramuscularly such that the transgene is expressed, wherein the adeno-associated viral vector is free of helper adenovirus contamination. It is noted that although the claims of the instant application recite characteristic of the adeno-associated viral composition as

prepared by cesium chloride centrifugation, this limitation would still encompass a composition free of helper adenovirus vector and also because same method of purification is used in both the application. As such, the claims of the co-pending application 09/237,064 make obvious the instantly claimed method and AAV vectors comprising the ApoE gene.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 7-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-24 and 26-28 of co-pending Application No. 09/242,977. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method for expressing a transgene (ApoE in the co-pending application) in an animal or in a cell or in a patient by introducing a composition comprising an adeno-associated viral vector comprising a transgene (ApoE encoding transgene in the co-pending application) into the cell such that the transgene is expressed in the cell, wherein the adeno-associated viral vector is free of helper adenovirus contamination. It is noted that although the claims of the co-pending application recite characteristic of the adeno-associated viral composition as prepared by four rounds of cesium chloride centrifugation, this limitation would still encompass a composition free of helper adenovirus vector because both the applications disclose four rounds of cesium chloride gradient centrifugation for the adeno-associated virus composition. As such, the claims of the co-pending application 09/242,977 make obvious the instantly claimed method and AAV vectors.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 7-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Podsakoff et al (US 5,858,351, 1-12-1999, filing date 1-18-1996, ref. # AI in the IDS filed 3-16-01).

Podsakoff et al teach a rAAV for gene therapy wherein the gene encoding erythropoietin is under the control of the CMV immediate early promoter, has SV40 polyadenylation sequences at the 3' end, and these sequences are flanked by 5' and 3' AAV ITRs (see materials and methods section in col 16 continued in col 17. They also teach that RSV promoter and other promoters can also be used for driving the expression of the gene of interest. They teach to purify the rAAV preparation by cesium chloride isopyknic gradient centrifugation and isolating the bands with average density of approximately 1.38 g/ml. Podsakoff et al also teach to inject the rAAV vector in mice intramuscularly in heart and cardiac muscles (see col 19 continued in col 20) and that erythropoietin is secreted by the myotubes or myoblasts. Podsakoff further teach that EPO gene was used as an example and that other suitable DNA sequences could be used that encode for proteins used for the treatment of different diseases (see lines 31-67 in column 10).

Therefore, the invention of claims 7-11 is anticipated by Podsakoff et al.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Podsakoff et al (US 5,858,351, 1-12-1999, filing date 1-18-1996, ref. # AI in the IDS filed 3-16-01) in view of Kashyap et al. (Journal of Clinical Investigation 96:1612-1620, ref# CU in the IDS filed 3-16-01).

Podsakoff et al teach a rAAV for gene therapy wherein the gene encoding erythropoietin is under the control of the CMV immediate early promoter, has SV40 polyadenylation sequences at the 3' end, and these sequences are flanked by 5' and 3' AAV ITRs (see materials and methods section in col 16 continued in col 17. They also teach that RSV promoter and other promoters can also be used for driving the expression of the gene of interest. They teach to purify the rAAV preparation by cesium chloride isopyknic gradient centrifugation and isolating the bands with average density of approximately 1.38 g/ml. Podsakoff et al also teach to inject the rAAV vector in mice intramuscularly in heart and cardiac muscles (see col 19 continued in col 20) and that erythropoietin is secreted by the myotubes or myoblasts. Podsakoff further teach that EPO gene was used as an example and that other suitable DNA sequences could be used that encode for proteins used for the treatment of different diseases (see lines 31-67 in column 10). Podsakoff et al does not teach an rAAV vector composition comprising 5' ITR, nucleic acid sequence encoding ApoE, and 3'ITR, wherein the level of contaminating adenoviral helper virus is no greater than that obtained by subjecting said recombinant rAAV to four rounds of cesium chloride centrifugation.

Kashyap et al teach that genetic dyslipoproteinemias are ideal candidates for gene therapy since the molecular defects in the genes have been established and many of the diseases have significant sequelae to warrant treatment including premature cardiovascular and peripheral vascular disease or recurrent pancreatitis and pancreatic insufficiency (see the first paragraph in the section on discussion on page 1618). These investigators selected the apoE-deficient model to determine

the feasibility of apolipoprotein gene replacement and prevention of atherosclerosis in mice with ApoE deficiency by providing the mice with an ApoE adenoviral vector intravenously. They also teach an ApoE adenoviral vector from which ApoE cDNA can be spliced out (see methods section on page 1613).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the rAAV vector of Podsakoff et al by cloning the ApoE cDNA taught by Kashyap et al e al, produce composition of the virus, purify it be cesium chloride centrifugation and use the resultant composition for delivery of ApoE gene to animals with reasonable expectation of success because all the pertinent methods are taught by Podsakoff et al and the cDNA for ApoE is taught by Kashyap et al. An artisan would have been motivated to use rAAV based method for ApoE gene delivery to treat atherosclerosis because Podsakoff et all teach that rAAV vector method is unique because of its ability to transduce non-proliferating cells along with the attributes of being inherently defective and nonpathogenic and because it is art recognized that adenovirus mediated gene delivery causes immune response (see lines 50-67 in column 1 of Podsakoff et al). With regard to claim limitations directed to specific titers of rAAV, it is noted that such an embodiment is sufficiently made obvious by the cited prior art of record in light of the state of the art as well as the level of skill of those in the art with regard to optimization parameters. For example, Podsakoff et al. teach the determination of effective dose range for rAAV vectors in Example 1. In particular, in Example 4, Podsakoff et al. teach i.m. injection into mice of rAAV-hEPO at 3×10^{11} vector genomes.

13. Claims 7-10 and 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Podsakoff et al 1999 in view of Fang et al 1995 (Fang B et al Human Gene Therapy 6:1039-1044, 1995, ref. # CS in the IDS filed 3-126-01) and Kay et al (US 5,980, 886, 11-9-1999).

The teachings of Podsakoff et al have been previously described in paragraph 12 above. Podsakoff et al also teach that their vector and method can be used for treatment of endocrine, metabolic, hematologic and other disorders including various blood disorders such as anemias, thalassemia and hemophilia (see

lines 31-42 in col 10). They also discuss the drawbacks of using adenoviral vectors for gene therapy, such as the elicitation of immune response to viral proteins which would preclude subsequent treatments. Podsakoff et al does not teach adeno-associated virus vectors comprising transgenes encoding factor IX, beta-interferon, insulin, erythropoietin, growth hormone, and parathyroid hormone.

Fang et al teach gene therapy of hemophilia B using adenovirus mediated factor IX expression (see the abstract). They also teach that adenovirus mediated gene transfer in vivo results in only transient gene expression due to the destruction of adenovirally transduced cells by the host immune system (see first para of the introduction section). Fang et al also teach an adenoviral vector that contains the cDNA encoding factor IX protein (materials and methods section on page 1040).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the rAAV vector of Podsakoff et al by cloning the factor IX cDNA in it and use the resultant vector in gene therapy of hemophilia by injecting with reasonable success because the methods of making rAAV vector and gene delivery in muscles are taught by Podsakoff while Fang et al teach a factor IX vector from which the factor IX cDNA sequences can be spliced out. An artisan would have been motivated to use an adeno-associated viral vector in place of adenoviral vector because Fang et al teach that adenoviral vector mediated gene delivery results only in transient gene expression due to immune response and therefore, an artisan would have used an alternative method of gene therapy.

Regarding the other proteins recited in claim 9, it is noted that the time of the invention, the cDNAs encoding the recited proteins were known in the art and were subject of preparing vectors for expression of these proteins. For example, Kay et al (US 5,980, 886, 11-9-1999) taught at vector for expression of proteins in liver and they listed insulin, growth hormone, erythropoietin, ApoE, parathyroid hormone, interferons, and several other proteins that could be expressed using their vector system. Therefore, an artisan would have been able to make recombinant AAV expressing recited proteins, such as insulin, growth hormone, erythropoietin, ApoE, parathyroid hormone, interferons, at the time of the claimed

invention with a reasonable expectation of success. An artisan of skill would have been motivated to make such vectors because all these proteins were known to be associated with a disease therefore, making such vectors would have helped in devising and developing therapeutic strategies.

14. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER